

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> A61K 9/127, 31/70, 38/00, C07H 21/00, C07K 1/00, 1/13, 2/00, C12N 5/00, C12Q 1/68	<b>A1</b>	<b>(11) International Publication Number:</b> WO 98/53801 <b>(43) International Publication Date:</b> 3 December 1998 (03.12.98)
<b>(21) International Application Number:</b> PCT/US98/10804 <b>(22) International Filing Date:</b> 28 May 1998 (28.05.98) <b>(30) Priority Data:</b> 08/864,765 28 May 1997 (28.05.97) US <b>(71) Applicant (for AM AZ BY KG KZ MD RU TJ TM only):</b> ISIS PHARMACEUTICALS, INC. [US/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US). <b>(71)(72) Applicant and Inventor:</b> NIELSEN, Peter, E. [DK/DK]; Hjortevanget 509, DK-2980 Kokkedal (DK). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> KNUDSEN, Helle [DK/DK]; Raadmandsgade 50 A, 4. tv, DK-2200 Copen- hagen Ø (DK). <b>(74) Agents:</b> CALDWELL, John, W. et al.; Woodcock Washburn Kurtz Mackiewicz & Norris LLP, 46th floor, One Liberty Place, Philadelphia, PA 19103 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** CONJUGATED PEPTIDE NUCLEIC ACIDS HAVING ENHANCED CELLULAR UPTAKE**(57) Abstract**

Peptide nucleic acids conjugated to lipophilic groups and incorporated into liposomes exhibit enhanced cellular uptake and distribution. Cellular uptake and distribution of peptide nucleic acids also increases with the introduction of an amino acid side chain into the backbone of peptide nucleic acids. Methods of modulating cellular uptake and methods for treating animals are provided. The peptide nucleic acids of the invention comprise naturally-occurring nucleobases and non-naturally-occurring nucleobases attached to a polyamide backbone.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/10804

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/450; 435/6, 325, 375; 514/2, 44; 530/300, 333; 536/23.1, 24.3, 24.5, 25.3, 25.32; 568/818

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,539,082 A (NIELSEN et al.) 23 July 1996, column 2, line 65 to column 11, line 9.	1-52
A	WO 97/14026 A2 (LANSDORP) 17 April 1997, page 6, lines 18-24, page 8, line 33 to page 9, line 6, page 10, lines 27-35.	1-52
A	Amine Reactive Fluorescent Probes: Offering a selection of succinimidyl esters, isothiocyanates and sulfonyl halides. Pierce ImmunoTechnology Catalog and Handbook. 1992, page E-65.	1-52



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 AUGUST 1998

Date of mailing of the international search report

16 SEP 1998

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/10804

## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6): A61K 9/127, 31/70, 38/00; C07H 21/00; C07K 1/00, 1/13, 2/00; C12N 5/00; C12Q 1/68

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL : 424/450; 435/325, 375; 514/2, 44; 530/300, 333; 536/23.1, 25.3, 25.32

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN (BIOSIS, CAPLUS, CJACS, INPADOC, MEDLINE, REGISTRY, WPIDS)

Search Terms: peptide nucleic acid, PNA, adamantoyl, fluoroscein, lysine, lipophilic, uptake, label, conjugate, Nielsen, Peter E.

## PATENT COOPERATION TREATY

PCT

REC'D 23 FEB 1999

INTERNATIONAL PRELIMINARY EXAMINATION REPORT PCT


(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ISIS-3045	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/10804	International filing date (day/month/year) 28 MAY 1998	Priority date (day/month/year) 28 MAY 1997
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant NIELSEN, PETER E.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 0 sheets.

## 3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  04 DECEMBER 1998	Date of completion of this report  04 FEBRUARY 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  THOMAS G. LARSON, PH.D. 
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/10804

## I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

☒ the international application as originally filed.

☒ the description, pages 1-47 , as originally filed.

pages NONE , filed with the demand.

pages NONE , filed with the letter of \_\_\_\_\_.

pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

☒ the claims, Nos. 1-52 , as originally filed.

Nos. NONE , as amended under Article 19.

Nos. NONE , filed with the demand.

Nos. NONE , filed with the letter of \_\_\_\_\_.

Nos. \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

☒ the drawings, sheets/fig 1 , as originally filed.

sheets/fig NONE , filed with the demand.

sheets/fig NONE , filed with the letter of \_\_\_\_\_.

sheets/fig \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE .

☒ the claims, Nos. NONE .

☒ the drawings, sheets/fig NONE .

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/10804

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)

Claims 1-52

YES

Claims NONE

NO

Inventive Step (IS)

Claims 1-52

YES

Claims NONE

NO

Industrial Applicability (IA)

Claims 1-52

YES

Claims NONE

NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1-52 are the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest compounds of the structure with groups Ri and Rj as claimed, or methods of making and using the compounds.

----- NEW CITATIONS -----

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/10804

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

~~Sheet 10~~

**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): A61K 9/127, 31/70, 38/00; C07H 21/00; C07K 1/00, 1/13, 2/00; C12N 5/00; C12Q 1/68 and US Cl.: 424/450; 435/325, 375; 514/2, 44; 530/300, 333; 536/23.1, 25.3, 25.32



## PATENT COOPERATION TREATY

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## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

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in its capacity as elected Office

Date of mailing (day/month/year) 08 January 1999 (08.01.99)	
International application No. PCT/US98/10804	Applicant's or agent's file reference ISIS-3045
International filing date (day/month/year) 28 May 1998 (28.05.98)	Priority date (day/month/year) 28 May 1997 (28.05.97)
Applicant NIELSEN, Peter, E. et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

04 December 1998 (04.12.98)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer N. Fischer Telephone No.: (41-22) 338.83.38
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